DETAILED ACTION

The receipt is acknowledged of applicants' IDS filed 02/25/2011, IDS filed 03/18/2011, and request for RCE filed 02/25/2011.

Claims 1, 4-9, 11 and 13 previously presented.

Claims 4, 8, 9 are currently canceled and claims 17-22 are currently added.

Claims 1, 5-7, 11, 13, and 17-22 are pending.

Election/Restrictions

1. Newly submitted claim 17 and 19 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claims are directed to single adhesive layer preparation comprising styrene-isobutylene-styrene block copolymer and ultra-pale rosin ester, while previously prosecuted claim 13 is directed to liquid reservoir type preparation which is distinct from adhesive single layer preparation. Claims to the different species recite the mutually exclusive characteristics of such species, in addition, these species are not obvious variants of each other based on the current record. There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The Species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely

to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 17 and 19 withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1, 5-7, 11, 13, 18, 20-22 are included in the prosecution.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/25/2011 has been entered.

Priority

3. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1, 5-7, 11, 13, 18, 20-22 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 10, 12-17, 19 and 20 of copending Application No. 11/815,499. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter claimed in the instant application is fully disclosed in the referenced copending applications and would be covered by any patent granted on the copending applications since the referenced copending applications and the instant application are claiming common subject matter as follows: transdermal preparation containing 4-(2-methyl-l-imidazoolyl)-2,2-diphenylbutylamide. The present claims and the co-pending claims are obvious over each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

6. The examiner acknowledges applicants' request to hold the provisional double patenting rejection in abeyance till the rejection is the only rejection remaining in the present application and allowable subject matter is indicated. However, as applicants realize, "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications. If the "provisional" double patenting rejection in

one application is the only remaining rejection in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other applicant into a double patenting rejection at the time the one application issues as a patent. **MPEP § 804, subsection I.B**. Therefore, the double patenting rejection is hereby maintained.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 21 and 22 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating increased urinary frequency or urinary incontinence in patients with overactive bladder, comprising administering a therapeutically effective amount of 4-(2-methyl- 1- imidazolyl)-2,2-diphenylbutylamide or a medically acceptable salt thereof, does not reasonably provide enablement for preventing such conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: the nature of the invention; the breadth of the claims; the state of the prior art; the relative skill of those in

the art; the amount of direction or guidance presented; the predictability or unpredictability of the art; the presence or absence of working examples; and the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The nature of the invention: The nature of the invention is a method for preventing or treating increased urinary frequency or urinary incontinence in patients with overactive bladder, comprising administering a therapeutically effective amount of transdermal preparation containing 4-(2-methyl- 1- imidazolyl)-2,2-diphenylbutylamide or a medically acceptable salt thereof.

The breadth of the claims: The claims are broad. The claims encompass prevention of increased urinary frequency or urinary incontinence in susceptible patients having overactive bladder, and the burden of enabling prevention of symptoms before they actually occur would be greater than that of enabling a treatment due to the need of additional testing and screening to those humans susceptible to develop such symptoms. The prevention of increased urinary frequency or urinary incontinence may or may not be addressed by the administration of the instant composition.

The state of the prior art: The state of the art does not recognize the administration of compositions to prevention of increased urinary frequency or urinary incontinence. The state of the art recognizes the treatment of such symptoms when they happen, but not their cure. See the article by Miyachi et al. (“Synthesis and Antimuscarinic Activity of a Series of 4-(1-Imidazolyl)-2,2-diphenylbutyramides:

Discovery of Potent and Subtype-selective Antimuscarinic Agents", IDS filed 01/31/2006).

The relative skill of those in the art: The relative skill of those in the art is high.

The amount of direction or guidance presented: There is no guidance given by the specification on how to prevent of increased urinary frequency or urinary incontinence before they happen. Guidance for treatment of overactive bladder is provided, but not its prevention and prevention of its symptoms before they happen. Administering such muscarinic receptors antagonist drug will affect smooth muscles in the body that may not be needed. It is not obvious from the disclosure of treating overactive bladder if the symptom will be prevented before it happen because it may not happen at all, and one cannot predict the occurrence of disease or symptom. Administering muscarinic receptors antagonist will affect smooth muscles in many organs in the body and may provide un-needed side effects for patients that do not need such treatment.

The predictability or unpredictability of the art: The lack of significant guidance from the specification or prior art with regard to completely preventing symptoms of overactive bladder using the instant composition makes practicing the claimed invention unpredictable in terms of the prevention of the symptoms that may not happen and giving muscarinic receptors antagonist may only provide the patient with un-needed and unwanted effect of such drugs.

The presence or absence of working examples: No working examples to show preventing of symptoms of overactive bladder or even treating and curing overactive bladder.

The quantity of experimentation necessary: Therefor, the practitioner would turn to trial and error experimentation to practice the instant method for treating overactive bladder symptoms without guidance from the specification or the prior art. Therefore, undue experimentation becomes the burden of the practitioner.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1, 5-7, 11 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over the article by Miyachi et al. (“Synthesis and Antimuscarinic Activity of a Series of 4-(1-Imidazolyl)-2,2-diphenylbutyramides: Discovery of Potent and Subtype-selective Antimuscarinic Agents”, IDS filed 01/31/2006), in view of the article by Gupta et al. (“New Perspectives on the Overactive Bladder: Pharmacokinetics and Bioavailability", currently provided) and further in view of either Versi et al. (US 2003/0190072, of record) or Landau et al. (US 6,846,823, record).

Applicant Claims

Currently amended claim 1 is directed to a transdermal preparation containing 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutylamide or a medically acceptable salt thereof, and an external preparation base.

Currently amended claim 11 is directed to a transdermal preparation for treating increased urinary frequency and urinary incontinence containing 4-(2-methyl-1-

imidazolyl)-2,2-diphenylbutylamide or a medically acceptable salt thereof, an external preparation base and a structural body.

Determination of the Scope and Content of the Prior Art

(MPEP §2141.01)

Miyachi teaches that the inhibitory action of 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutylamide (KRP-197) on bladder contractions is 15-19 times more potent than oxybutynin and with a similar duration of action (p 1157, col.1, ¶ 2). KRP-197 is fivefold more selective for bladder than oxybutynin (p 1157, col.2, ¶ 2),

Ascertainment of the Difference Between Scope the Prior Art and the Claims

(MPEP §2141.012)

Miyachi however is silent regarding dosage forms and routes of administration of KRP-197.

Gupta teaches that transdermal delivery of antimuscarinic drugs to treat overactive bladder bypasses presystemic liver and gastrointestinal metabolism and decreases metabolite formation and reduces dry mouth (see entire document, and in particular the paragraph bridging page 79 and 80).

Versi teaches treating of varieties of incontinence-related conditions using antimuscarinic agents including KRP-197 (abstract; paragraphs 0010, 0016; table 2; claim 27). The active agents can be administered by means of transdermal patch using conventional technology in order to reduce side effects and obtain improved subject

compliance (paragraph 0070). Transdermal patches may contain adhesive reservoir containing the drug dissolved and/or dispersed in the adhesive (paragraph 0080). The teaching of Versi of dissolved and/or dispersed drug in the reservoir meets the limitation of claim 9 that drug is dissolved and non-dissolved.

Landau teaches treating at least one symptoms of lower urinary tract disorder including urinary frequency, urgency, incontinence, nocturia and enuresis using composition comprising antimuscarinic including KRP-197 (abstract; col.18, lines 38-43; col.20, line 18). The composition can be transdermal composition delivered from patch that provides controlled release of the drug through the skin for long period from one application (col.38, lines 40-42, 50-55). Transdermal patch comprises laminate structure comprising backing layer, release liner, and liquid reservoir containing the drugs and permeation enhancer (col.45, lines 5-43).

Adhesive taught by Versi and Landau and permeation enhancer taught by Landau read on the claimed external preparation means because according to applicants' disclosure on page 15, lines 1-7, "external preparation base" can be amphipathic solubilizing agent, a suspension base, a softener, an emulsifier, a buffer, a transdermal permeability enhancer, a tackifier, a tackiness enhancer, an adhesive, a skin irritancy mitigator, and an additive.

Finding of Prima Facie Obviousness Rational and Motivation

(MPEP §2142-2143)

At the time of the invention it was known that KRP-197 is antimuscarinic drug that is more potent than other antimuscarinic drugs known as this time such as oxybutynin as taught by Miyachi. At the time of the invention Gupta preferred transdermal delivery of antimuscarinic drugs that treat overactive bladder to bypass presystemic liver and gastrointestinal metabolism and decreases metabolite formation and reduces dry mouth. It was further known at the time of the invention that KRP-197 can be delivered in transdermal devices as taught by both of Versi and Landau.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention treat overactive bladder using KRP-197 as taught by Miyachi and deliver the drug transdermally as taught by Gupta, Versi and Landau. One would have been motivated to do so because Gupta teaches that transdermal delivery of antimuscarinic drugs to treat overactive bladder bypasses presystemic liver and gastrointestinal metabolism and decreases metabolite formation and reduces dry mouth. One would further be motivated to deliver KRP-197 utilizing transdermal device because both of Versi and Landau teaches that KRP-197 can be delivered from transdermal devices that provides reduced side effects, improved patient compliance and controlled release of the drug. One would reasonably expect formulating transdermal device comprising KRP-197 that delivers the drug in a controlled manner to treat urinary bladder disorders effectively with minimal undesired side effects and improved patient compliance.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the

instantly claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

13. Claims 13, 18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyachi et al. in view of Gupta and either Versi et al. or Landau et al. as applied to claims 1, 4-9 and 11, and further in view of Luo et al. (US 6,586,000, of record).

Applicant Claims

Claim 13 is further recite the structure of the transdermal device comprising a reservoir type preparation, wherein 4-(2-methyl-l-imidazolyl)-2,2-diphenylbutylamide is present in a mixture with one or more of the external preparation bases; and wherein the structural body comprises a membrane for controlling drug permeation, an adhesive layer, a support, and a peelable liner. Claims 18 and 20 recites that the reservoir comprises HPMC and ethanol/water mixture.

Determination of the Scope and Content of the Prior Art

(MPEP §2141.01)

The combined teaching of Miyachi, Gupta, and either one of Versi or Landau are discussed above. The combination of the references teaches transdermal device comprising KRP-197, and Landau further teaches transdermal device comprising liquid reservoir, backing layer and peelable release liner.

Ascertainment of the Difference Between Scope the Prior Art and the Claims

(MPEP §2141.012)

The references however, do not teach the structure of the transdermal device to comprise a reservoir, a membrane to control the release of the drug and the adhesive layer as claimed by claim 13, or the composition of the reservoir as claimed by claims 18 and 20.

Luo teaches transdermal device comprising reservoir containing active agent in aqueous gel preparation. The aqueous preparation comprises water, ethanol and HPMC. The device comprises backing layer, release liner, skin contact adhesive and rate controlling membrane to control the rate at which the drug permeates out of the device (col.4, lines 15-33; col.21, lines 50-55; col.22, lines 34-44; col.24, lines 16, 60-67; col.25, lines 41-43; col.26, lines 10-15). The skin contact adhesive maintains the device in transmitting relationship to the body surface (col.4, lines 27-30).

Finding of Prima Facie Obviousness Rational and Motivation

(MPEP §2142-2143)

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention treat overactive bladder using KRP-197 delivered from transdermal device comprising liquid reservoir containing the drug, backing layer and peelable release liner as taught by the combination of Miyachi, Gupta, and Versi or Landau and replace the liquid reservoir with aqueous preparation comprising water, ethanol and HPMC, and further add a rate controlling membrane and skin contact adhesive to the

device as taught by Luo. One would have been motivated to do so because Luo teaches such aqueous reservoir material is suitable for transdermal drug delivery and the rate controlling membrane controls the rate at which the drug permeates out of the device and the skin contact adhesive layer maintains the device in transmitting relationship to the body surface. One would reasonably expect formulating transdermal device comprising KRP-197 in reservoir comprising water, ethanol and HPMC and having backing layer and peelable release liner and further has rate controlling membrane and skin contact adhesive layer wherein the device deliver the drug to the skin in a controlled manner while being secured to the skin of the user.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

14. Applicant's arguments see page 8 and 9 of amendment and argument filed 02/25/2011, with respect to date of Nitti's reference have been fully considered and are persuasive. The obviousness rejection based on Nitti has been withdrawn. New ground of rejection has been issued.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis A. Ghali whose telephone number is (571) 272-

0595. The examiner can normally be reached on Monday-Thursday, 6:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on (571) 272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Isis A Ghali/
Primary Examiner, Art Unit 1611

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